Association between midlife dementia risk factors and longitudinal brain atrophy: the PREVENT-Dementia study

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The PREVENT-Dementia study

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ABSTRACT

Background: Increased rates of brain atrophy on serial MRI are frequently used as a surrogate marker of disease progression in Alzheimer's disease and other dementias. However, the extent to which they are associated with future risk of dementia in asymptomatic subjects is not clear. In this study, we investigated the relationship between the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) risk score and longitudinal atrophy in middle aged subjects.

Materials and Methods: A sample of 167 subjects (aged 40-59 at baseline) from the PREVENT-Dementia programme underwent MRI scans on two separate occasions (mean interval 735 days; SD 44 days). We measured longitudinal rates of brain atrophy using the FSL Siena toolbox.

Results: Annual percentage rates of brain volume and ventricular volume change were greater in those with a high (>6) vs low CAIDE score – absolute brain volume percentage loss 0.17% (CI 0.07 – 0.27) and absolute ventricular enlargement 1.78% (CI 1.14 – 2.92) higher in the at risk group. Atrophy rates did not differ between subjects with and without a parental history of dementia, but were significantly correlated with age. Using linear regression, with covariates of age, sex, and education, CAIDE score > 6 was the only significant predictor of whole brain atrophy rates (p=0.025) whilst age (p=0.009), sex (p=0.002), and CAIDE > 6 (p=0.017) all predicted ventricular expansion rate.

Conclusion: Our results show that progressive brain atrophy is associated with increased risk of future dementia in asymptomatic middle aged subjects, two decades before dementia onset.

INTRODUCTION

It is now clear that pathological changes related to Alzheimer's disease start decades before cognitive symptoms are evident.[1, 2] Dementia prevention or postponement strategies, such as lifestyle changes, should therefore begin as early as possible and there is a need to identify at risk individuals in whom such interventions are likely to have the greatest effect. Alzheimer's disease shares risk factors with vascular disease such as hypertension and obesity, and these can be used both to identify individuals at risk, and act as modifiable intervention targets.

A number of dementia risk scores have been suggested [3] including the CAIDE [4] score, which was developed in middle aged community dwelling subjects.

Cross sectional studies have found associations between raised midlife dementia risk scores and reduced brain volume.[5-8] There has, however, been little reported research on the relationship between dementia risk score and subsequent brain atrophy. The aim of this study was to investigate to what extent an increased CAIDE score in midlife was linked to greater rate of brain atrophy over subsequent years. This is important to determine, since brain volume change is a frequently utilised objective biomarker of disease progression used in dementia studies, especially for Alzheimer's disease. It is therefore important to know whether it may also be useful as a putative outcome marker for disease progression in midlife subjects.

METHODS

Subjects

The protocol has been described in detail elsewhere.[9] A total of 193 participants aged 40 to 59, of whom 168 had repeat MRI were recruited through multiple sources. Initially they were identified from the dementia register database held at a London National Health Service (NHS) Trust, part of the UK National Health Service. This registry holds information on patients with dementia and cognitive impairment who have consented to be approached for clinical research and their carers (often offspring). Other participants were recruited via the Join Dementia Research website (https://www.joindementiaresearch.nihr.ac.uk/), through information about the study on the Internet and public presentations. The study aimed to recruit approximately half of the subjects with a parental family history of dementia and half without. For those with a family history, the estimated time to dementia onset was on average 20 years, based on age of parental dementia onset.[9]

Dementia Risk Score

Dementia risk scores were calculated for each participant at baseline using the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) score.[4] This is a dementia risk score composed of weightings by reference to the following variables: age, sex, education, systolic blood pressure, body mass index (BMI), total cholesterol, physical activity, and apoE status. Scores vary from 0 to 18. We treated this as a binary variable, split according to the group median (DRS <=6). Family history of dementia was defined as positive if at least 1 parent had clinically diagnosed dementia and apoE4 status was regarded as positive for >= 1 ε4 allele.

Imaging

Participants underwent multimodal 3 T structural magnetic resonance imaging on a single scanner (Siemens Verio) including volumetric T1-weighted scans (176 slices, 1.0 × 1.0 mm, 1.0 mm slice

thickness, repetition time = 2300 ms, echo time = 2.98 ms, flip angle 9°). Scans were repeated after approximately 2 years on the same scanner using the same protocol.

Percentage brain volume change and ventricular enlargement between the two scans, were determined using the FSL siena program (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki).[10] Values were then divided by the time between scans to give rates per year. Total intracranial volume (ICV) was calculated from the sum of grey matter, white matter and CSF segmentation done with SPM12 (http://www.fil.ion.ucl.ac.uk/spm). All output was manually checked to ensure correct brain segmentation, and alignment of baseline / repeat scans.

Statistical analysis

Brain volume data and clinical variables were analysed with the Statistical Package for Social Sciences (SPSS version 19). Independent t-tests were used to compare groups for continuous variables and chi squared test for categorical data. Pearson's correlation coefficient was used to compare continuous variables. Linear regression was used to investigate predictors of brain atrophy rates. Residuals were checked by eye to verify normality, heteroscedasticity and absence of non linear associations.

Consent and organization of examinations

Participants were seen at the West London Cognitive Disorders Treatment and Research Unit. Blood was taken for apolipoprotein E (APOE) genotyping, with all members of the research and clinical teams remaining blind to the result. Approval for the study has been given by the NHS Research Ethics Committee London Camberwell St-Giles (REC reference: 12/LO/1023). All participants provided informed written consent.

Role of the funding source

The sponsor had no role in study design, collection, analysis or interpretation of data, nor in the writing of the report or decision to submit the paper for publication.

RESULTS

Of the 193 participants with T1 MR scans at baseline, 168 had a repeat scan. There were no significant differences between those with versus without a repeat scan in age (52.0 SD 5.4 vs 51.3 SD 5.4; t_{191}=0.6, p=0.5), years of education (16.1 SD 3.4 vs 14.7 SD 3.1; t_{191}=1.9,p=0.06) , CAIDE score (5.9 SD 2.9 vs 5.7 SD 2.9; t_{189}=0.4,p=0.7), sex (118/168 vs 17/25 female; χ^2=0.1, p=0.8), or APOE genotype (64/166 vs 6/25 with ε4; χ^2=2.0, p=0.16). However, those with repeat imaging were more likely to have a parent with dementia (89/168 [53 %] vs. 6/25 [24 %]; χ^2=7.3; p=0.007).

One participant had marked ventricular shrinkage (-26%) between baseline and repeat scan. There were no obvious technical problems with this participant's images. As this ventricular change was more than 3 SD below the mean (+3.6% SD 5.8), this subject was excluded from further analysis. Demographic details of the 167 participants included in the longitudinal analysis are shown in table 1.

In univariate analyses, there were no significant differences in either ventricular enlargement or brain volume change rates between those with versus without a parent with dementia (table 2), or between those with vs. without presence of the APOE ε4 allele. Age (table 3) was significantly associated with both ventricular enlargement and brain volume change, as was having CAIDE score > 6. Males had greater rate of ventricular enlargement, but no difference in overall brain volume change.

In a linear regression, including covariates of age, sex, and number of years of education, ventricular enlargement was greater in those with CAIDE score > 6, older age at baseline, and male sex (table 4, figure 1).

In the linear regression for brain volume change, CAIDE score > 6 was the only significant predictor (table 4), although age was borderline significant.

DISCUSSION

We found, in this group of middle aged subjects, that having a CAIDE dementia risk score over 6 was significantly associated with brain atrophy over a two year period, after controlling for age, sex and years of education. The presence of the APOE ε4 allele, or a parent with dementia was not related to ongoing brain atrophy.

Previous studies, using this and other cohorts, have demonstrated significant associations between CAIDE and brain volume.[5, 6] Data from the Framingham study [11] investigated the effect of individual risk factors, and found midlife diabetes associated with faster hippocampal atrophy, rated visually. A study with MRI taken up to 30 years apart found midlife CAIDE score associated with longitudinal medial temporal lobe atrophy.[12] Neither of these showed strong associations with total brain volume, however the brain boundary shift technique we utilised is more sensitive to longitudinal change than individual volume measurement.[13]

We found relatively greater ventricular expansion in male vs female participants. We could not find any previous analysis of the effect of sex on ventricular expansion using the siena technique, however one paper using ventricular thickness found greater longitudinal expansion in male subjects[14] and there have been reports of differential trajectories of brain volume changes between the sexes in a number of structures.[15] Men generally have larger ventricles [16] and it could be that either the ventricular enlargement is easier to detect in bigger ventricles (due to fewer partial

volume effects) or that enlargement is not a linear process, and is greater in bigger ventricles. Further research is suggested to verify this finding, and determine the causal factors.

We did not find an association between APOE ε4 and brain atrophy. A recent large study of amyloid deposition and cortical thinning,[17] found that middle aged APOE e4 carriers had markedly increased rates of amyloid deposition, but that the effect on cortical thinning was minimal. A separate cross-sectional study also found that the effect of the APOE ε4 on brain volume was only evident in those aged over 60. Our findings are in keeping with these studies, suggesting that APOE ε4 predisposes individuals to the Alzheimer amyloid cascade, in which brain volume changes appear at a relatively late stage.[2]

In our analysis, there was a strong univariate association between age and brain atrophy, however, CAIDE score > 6 was significantly associated with brain atrophy even after controlling for the linear effect of age. A recent paper [18] compared the utility of different dementia risk scores in predicting dementia in the large community dwelling Rotterdam study. They concluded that age was the component which contributed most to the predictive ability of the scores. However, they were unable to assess the effect of age on the CAIDE score, since all of their participants were in the oldest age category of the scoring system. They comment that since the CAIDE score was developed in middle aged subjects, it may not be appropriate for use in the over 60 age group, since some factors such as BMI may be associated with risk in middle age, but protective in later life.[19]

A limitation of this study is that due to the relatively young age of the participants, the actual future incidence of dementia remains unknown. However, planned longitudinal follow-up should reveal to what extent the CAIDE score and brain atrophy relate to ongoing cognitive decline.

In summary, in order to investigate preventative strategies for dementia, it is necessary to identify at risk subjects years before the onset of clinical symptoms. Our results here, showing an association between raised CAIDE score in mid-life and longitudinal brain atrophy support the use of the CAIDE score in studies such as the FINGER trial [20] for this purpose. They also indicate that serial MRI may be

a putative outcome measure in future trials aimed at disease prevention, even in this relatively young and symptom-free group.

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DECLARATION OF INTERESTS

John T. O'Brien has no conflicts related to this study. Unrelated to this work he has received honoraria for work as DSMB chair or member for TauRx, Axon, Eisai, has acted as a consultant for Lilly, has received honorarium for talks from GE Healthcare and research support from Alliance Medical.

Michael J. Firbank has no conflicts of interest to declare.

Karen Ritchie has no conflicts of interest to declare

Katie Wells has no conflicts of interest to declare

Guy Williams has no conflicts of interest to declare

Craig W. Ritchie has no conflicts of interest to declare

Li Su has no conflicts of interest to declare

Table 1 Subject demographics. Mean (SD) [range] or n/N (%) for the 167 subjects included in the longitudinal MRI analysis.

Age at first scan	52.0 (5.4) [40:59]
Years education	16.1 (3.4) [0:24]
CAIDE [N=165]	5.9 (2.9) [0:15]
CAIDE > 6 [N=165]	71/165 (43%)
Female	117/167 (70%)
Parent with dementia	89/167 (53%)
APOE ε4 [N=165]	64/165 (39%)
Interval (days)	735 (44) [627:898]

CAIDE = Cardiovascular Risk Factors, Aging, and Dementia risk score

Table 2 Univariate comparison of annual percentage change in brain volume and percentage change of ventricle volume with demographic variables. Negative brain volume change and positive ventricular enlargement indicate brain atrophy.

	Percentage ventricular enlargement			Percentage brain volume change		
	No	Yes		No	Yes	
Male N= 50 / 167	1.42 (2.65)	3.04 (2.29)	t_{165} =-3.75; p<0.001 **	-0.004 (0.35)	0.027 (0.25)	t_{165} =-0.56; p=0.579
Parent with dementia N= 89 / 167	1.87 (2.47)	1.93 (2.81)	t_{165} =-0.14; p=0.889	-0.011 (0.32)	0.020 (0.33)	t_{165} =-0.62; p=0.537
APOE4 ε4 allele N= 64 / 164	1.88 (2.65)	1.95 (2.70)	t_{163} =-0.17; p=0.868	0.014 (0.34)	-0.018 (0.30)	t_{163} =0.62; p=0.534
CAIDE > 6 N= 71 / 165	1.14 (2.30)	2.92 (2.78)	t_{163} =-4.51; p<0.001 **	0.075 (0.31)	-0.096 (0.32)	t_{163} =3.46; p=0.001 **

** p < 0.01

CAIDE = Cardiovascular Risk Factors, Aging, and Dementia risk score

Table 3 Univariate correlations of annual percentage change in brain volume and percentage change of ventricle volume with demographic variables

	Age	Years of Education
Ventricular enlargement %	r= 0.31; p<0.001 **	r= 0.01; p=0.857
Brain volume change %	r= -0.25; p=0.001 **	r= 0.05; p=0.513

** $p < 0.01$

Table 4 Results of linear regression of annual ventricular enlargement rate and percentage brain volume change with age, years of education, sex, and CAIDE score> 6 as predictors

	Ventricular enlargement			Brain volume change		
	Standardised Beta	t	Sig.	Standardised Beta	t	Sig.
Age	0.217	2.660	0.009	-0.168	-1.941	0.054
Years education	0.102	1.411	0.160	-0.005	-0.064	0.949
Male Sex	0.226	3.131	0.002	0.107	1.397	0.164
CAIDE > 6	0.200	2.402	0.017	-0.200	-2.262	0.025

Ventricular enlargement Model: $F_{4,160} = 10.1$, $R^2 = 0.202$ (Adjusted $R^2 = 0.182$) $p<0.001$

Brain volume Model: Model: $F_{4,160} = 4.5$, $R^2 = 0.101$ (Adjusted $R^2 = 0.078$) $p=0.002$

CAIDE = Cardiovascular Risk Factors, Aging, and Dementia risk score

FIGURE CAPTIONS

Figure 1 Ventricular expansion as a function of age. Regression lines show linear fit for

Cardiovascular Risk Factors, Aging, and Dementia risk score (CAIDE) split by > 6.

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